

REMARKS

The continued examination of the current application is respectfully requested pursuant to 37 C.F.R. § 1.114 (RCE). Pursuant to this continued examination, it is respectfully requested that the above amendments be considered in view of the following remarks, and that all claims pending in this application be allowed.

Claims 10-20, 25-31, 79, 80, 82, 83, 85-92, 94, 95 and 97-120 are currently pending. Claims 79, 91 and 108 have been amended herein to recite the stimulation of specific immunity towards the papillomavirus. Claims 91 and 108 have been amended herein to delete the references to the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2. In accordance with this amendment, claims 99 and 111 have been deleted. New claims 121-123 have been added. These new claims are similar to claims 79, 91 and 108 except that they recite "consisting of" as the transition phrase and recite a pharmaceutically acceptable carrier.

Basis for these amendments and new claims may be found throughout the specification and claims as-filed, especially at page 3, lines 17-23. Applicants reserve the right to file a continuation or divisional application directed to any subject matter deleted by way of this Amendment.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 79, 80, 82, 83, 85, 87-92, 94, 95, 97-99, 101-111, and 113-120 are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the recitation of "consisting essentially of." The Office Action states that the specification is not clear as to the basic or novel characteristics of the claimed compositions.

To clarify the basic and novel aspects of the claimed subject matter, Applicants have amended claims 79, 91 and 108 herein to recite the stimulation of specific immunity towards the papillomavirus. New claims 121-123 have also been added, reciting the subject matter of independent claims 79, 91 and 108, using "consisting of" as a transitional phrase, as well as a pharmaceutically acceptable carrier. Thus, this rejection is obviated.

Rejections under 35 U.S.C. § 102(e)

Claims 79, 82, and 87-90 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Stanley *et al.* (U.S. Patent No. 6,096,869). The Examiner has maintained this rejection in light of the purported uncertainty concerning what ingredients are encompassed or excluded by the phrase "consisting essentially of." Applicants traverse.

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." Jamesbury Corp. v. Litton Industrial Products, Inc. 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). The cited reference does not describe or suggest all of the elements of the rejected claims as amended herein, and as discussed in greater detail below.

As noted above, independent claims 79, 91 and 108 have been amended herein to recite the stimulation of specific immunity towards the papillomavirus. This aspect of the claimed invention is not recited in the cited reference. Further, Applicants submit that new claims 121-123 are novel over the cited references, as these claims recite "consisting of" as the transitional phrase.

Thus, Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 91, 98, 99, 101-108, 110, and 115-120 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Stanley *et al.*, Galloway (*Infect. Agents & Disease* 3:187-193 (1994)), Hines *et al.* (*Obstet. and Gynecol.* 86(5):860-866 (1995)), and Gajewski (*J. Immunol.* 156:465-472 (1996)).

Claims 80, 81, 83-85, 92-97, 109, 113, and 114 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Stanley *et al.*, Galloway, Hines *et al.*, and Gajewski in further view of Crook *et al.* (*Cell* 67:547-556 (1991)) and Munger *et al.* (*EMBO J.* 8:4099-4105 (1989)).

Claims 80, 81, 83-85, 92-97, 109, 113 and 114 are rejected under 35 USC § 103 (a) as allegedly being unpatentable over Stanley *et al.* (US Patent 6,096,869), Galloway (1994, *Infectious Agents and Disease* 3:187-193), Hines *et al.* (1995, *Obstetrics and Gynecology* 86(5):860-866) and Gajewski (1996, *J. Immunol.* 156: 465-472), and further in view of Crook *et al.* (1991, *Cell* 67:547-556) and Munger *et al.* (1989, *EMBO J.* 8:4099-4105).

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

Turning to the primary reference, the Office Action maintains that Stanley *et al.* disclose the importance of administering a cytokine with a papillomavirus polypeptide composition. More specifically, the Office Action states that the data and tables presented in this document establish that cytokines are present in papillomavirus tissue pathologies and are a central aspect of papillomavirus infection. The Office Action asserts that, although Stanley *et al.* do not teach administering IL-2, the skilled artisan would have been motivated to treat papillomavirus infections by administering papillomavirus polypeptides with IL-2 in light of Hines *et al.* which disclose the administration of lymphocytes that are stimulated with various papillomavirus polypeptides and IL-2. Applicants traverse.

Stanley *et al.* disclose a comparison of cytokine expression profiles in healthy tissue as well as HPV-induced regressing and nonregressing lesions, and have discovered that IL-12 is present in 100 percent of regressing HPV-induced tumors, unlike many other cytokines also surveyed. Given the association between the presence of IL-12 in lesions resulting from HPV infection and the resulting regression of these lesions, Stanley *et al.* seek to increase the amount of IL-12 in an HPV-infected individual. However, Stanley *et*

al. do not disclose or suggest the importance of administering any cytokine other than IL-12 with a papillomavirus polypeptide. Indeed, it is evident from the text of both US Patent 6,096,869 and the corresponding international application WO96/29091 that Stanley *et al.* are limited to the use of IL-12 or its p40 subunit as a therapeutic material or as an adjuvant in the treatment of papillomavirus-associated lesions, eventually in combination with HPV polypeptides. There is no suggestion or reference to the replacement of IL-12 by another cytokine. Analysis of the data presented in Stanley *et al.*, with respect to IL-2 expression, clearly show that IL-2 transcripts are present in some non regressing warts (*see* Tables b and c), in 4 out of 5 regressing lesions (*see* Table d) as well as in normal cervix (*see* Table e). On the other hand, IL-12 p40 transcripts are present in all regressing lesions (*see* Table d) but absent in nonregressing warts (*see* Tables a and b) as well as in normal cervix (*see* Table e). Therefore, Applicants submit that Stanley *et al.* would not motivate the skilled artisan would have been motivated to treat papillomavirus infections by administering papillomavirus polypeptides with IL-2.

Concerning Hines, Applicants again submit that the technique disclosed in the cited reference does not concern that of the present invention and does not remedy the deficiencies of the other references. Hines *et al.* disclose the potential use of activated lymphocytes for therapeutic purposes. This cell-based strategy involves harvest of peripheral blood lymphocytes (PBL) from a patient with cervical carcinoma or from a histocompatible host, *in vitro* stimulation with early viral oncoprotein peptides (E6 and E7)

and exogenous recombinant IL-2. The activated cytotoxic T lymphocytes are then transferred back to the patient to achieve anti-tumor response.

Applicants stress that considerable practical difficulties must be overcome to practice this therapeutic approach including *ex vivo* culture and activation steps under good laboratory practice conditions, for each patient to be treated. Further, the reference discloses that effective anti-tumor responses require no or little down-regulation of MHC class I antigens. Thus, the Hines *et al.* approach further requires determination of MHC I status, and it is not known whether the cellular approach disclosed by Hines *et al.* would adequately provide effective treatment to eliminate HPV-induced lesions. Hines *et al.* neither disclose nor suggest the direct administration of IL-2 together with HPV polypeptides, but in fact teaches away from the present invention by suggesting that only explanted cells which have been activated *ex vivo* may be utilized to treat HPV-induced tumors.

Regarding Galloway, Applicants again note that this reference discusses various preclinical studies that have been performed with either late papillomavirus polypeptides recombinantly produced as fusion proteins (*see* page 190) or individual early papillomavirus polypeptide (*see* page 191). There is no suggestion in Galloway to combine the HPV polypeptides with a cytokine, in order to improve anti-papilloma immune response. In fact, Galloway reports an incomplete understanding of the relationship of papillomaviruses with the immune system, as discussed on page 191.

Regarding Gajewski, in the interest of expediting prosecution, claims 91 and 108 have been amended herein to delete the reference to the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2. Therefore, the rejection in view of Gajewski is mooted.

Applicants provide the following in further support of the differences between IL-2 and IL-12. As illustrated in the enclosed Summary Tables (from *Cytokines*, ed. Anthony Mire-Sluis & Robin Thorpe Eds., Academic Press (1998 pp. 526 and 532)), IL-2 and IL-12 exhibit a number of differences with respect to their protein structure, cellular sources and biological activities. IL-12 is a heterodimeric cytokine made up of two subunits (p35 and p40), important in defense against intracellular pathogens, as it induces IFN gamma production by T cells and NK cells, enhances NK and LAK activity to become cytolytic, and co-stimulates peripheral blood lymphocyte proliferation. The primary cellular source of IL-12 is the monocyte/macrophage lineage. In addition, B cells produce IL-12 but at a significantly lower level. With respect to IL-2, it is a monomeric protein that is produced exclusively by both CD4+ and CD8+ T lymphocytes. IL-2 exhibits a large variety of biological activities, including the stimulation of proliferation and differentiation of T cells, B cells, monocytes, and oligodendrocytes. IL-2 also promotes the cytolytic activity of activated T cells, and large granular lymphocytes. These inherent differences between the two cytokines fail to provide a reasonable expectation of success to one of ordinary skilled in the art that IL-2 administration together with HPV polypeptides would permit treatment of HPV infections.

Thus, none of the secondary references, Crook *et al.*, Munger *et al.* and Gajweski, remedy the deficiencies of the primary references.

In summary, Applicants submit that the cited references alone or in combination neither teach nor suggest the present invention and do not provide the skilled artisan with motivation to modify the invention or with an expectation of success. Thus, this rejection is obviated.

C O N C L U S I O N

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that the prosecution of this application may be expedited.

Respectfully submitted,

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